Influence of Medical Conditions and Lifestyle Factors on the Menstrual Cycle

Andrew S. Rowland,[1] Donna Day Baird,[1] Stuart Long,[2] Ganesa Wegienka,[1] Siobán D. Harlow,[3] Michael Alavanja,[4] and Dale P. Sandler[1]

Background. Few studies have described medical and lifestyle factors associated with various menstrual cycle characteristics.
Methods. We analyzed cross-sectional data collected from 3941 premenopausal women from Iowa or North Carolina participating in the Agricultural Health Study between 1994 and 1996. Eligible women were age 21–40, not taking oral contraceptives, and not currently pregnant or breast feeding. We examined four menstrual cycle patterns: short cycles (24 days or less), long cycles (36 days or more), irregular cycles, and intermenstrual bleeding.
Results. Long and irregular cycles were less common with advancing age and more common with menarche after age 14, with depression, and with increasing body mass index. The adjusted odds of long cycles increased with increasing body mass index, reaching 5.4 (95% confidence interval [CI] = 2.1–13.7) among women with body mass indexes of 35 or higher compared with the reference category (body mass index of 22–23). Smoking was associated with short cycles. Long cycles, irregular cycles, and intermenstrual bleeding were associated with a history of infertility. Having long cycles was associated with a doubling in the adjusted odds of having a fetal loss among women who had been pregnant within the last 5 years (odds ratio = 2.3; 95% CI = 0.9–5.7).
Conclusions. Menstrual patterns are influenced by a number of host and environmental characteristics. Factors that perturb menstruation may increase a woman's risk of other reproductive disorders.
(EPIDEMIOLOGY 2002;13:668–674)

Key words: menstrual cycle, menstruation, obesity, smoking, thyroid diseases, depression.

Menstrual cycle function is closely linked with a woman's fecundability or ability to become pregnant, and may affect her chronic disease risk.[1–4] For these reasons, clinicians and epidemiologists interested in women's health have proposed that menstrual cycle patterns provide a view into female reproductive biology. Despite the appeal of this paradigm,[5] only a handful of population-based studies have investigated "normal" menstrual function.[6–12] Because most of this research was based on college or graduate student populations, it is unclear how applicable the findings are to other populations. Also, few epidemiologic studies have examined the possible relation between menstrual cycle patterns and other reproductive outcomes.[2]

In this paper, we describe medical and lifestyle factors associated with menstrual cycle characteristics among 3941 menstruating women participating in a large study of the health of farm families. We also examine whether specific menstrual cycle characteristics are associated with having experienced a previous fetal loss or infertility.

From the [1]Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park; [2]CODA/Westat Inc., Durham, NC; [3]Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, MI; and [4]Epidemiology and Biostatistics Program, National Cancer Institute, Bethesda, MD.

Address correspondence to: Andrew S. Rowland, MPH Program, Department of Family and Community Medicine, UNM Health Sciences Center, 2400 Tucker NE, Albuquerque, NM 87131; arowland@salud.unm.edu

This research was funded by the intramural programs of the National Institute of Environmental Health Sciences and the National Cancer Institute.

Submitted 29 August 2001; final version accepted 21 May 2002.

DOI: 10.1097/01.EDE.0000024628.42288.8F

Methods

Study Population

The Agricultural Health Study is one of the largest studies of farm families ever conducted.[13] The study is being carried out in North Carolina and Iowa as a collaborative effort of the National Cancer Institute, the National Institute of Environmental Health Sciences, and the U.S. Environmental Protection Agency. The study was reviewed and approved by Institutional Review Boards at the National Institutes of Health, University of Iowa, and Battelle Life Sciences.

All participants provided informed consent. The study's methods have been described in detail.[14–15] Farmers who apply restricted pesticides to their crops or livestock must obtain state certification every 3 years. Anyone applying for certification in 1994 through 1996 was invited to enroll in the study; 63,572 private applicators were eligible. Of these, 52,399 (82%) enrolled by completing a brief questionnaire. Ninety-seven per cent (N = 51,037) were male. Of the male private applicators who enrolled, 42,452 (83%) were married. We asked married men (or men living with a female partner as married) to have their wives or partners enroll in the study by completing one questionnaire about their farm exposures and another about their reproductive health history.

Three-fourths of the wives/partners (N = 31289) enrolled in the study by completing the farm exposure questionnaire. We restricted the analysis to premenopausal women age 21–40 who were not pregnant or breast feeding and who were not taking oral contraceptives. Of the women who completed the exposure questionnaire, 11,310 were between the ages of 21–40. Fifty-seven per cent of the women in this age group (N = 6451) also completed the reproductive questionnaire. We excluded 1376 women who were currently taking oral contraceptives, 516 who were currently pregnant or breast feeding, 348 who reported having started menopause or were not sure whether they had started menopause, and 270 women whose records were missing data on the menstrual outcomes of interest. The remaining 3941 women were included in this analysis.

Assessment of Menstrual Cycle Characteristics

The menstrual questions were included as part of a reproductive history. Because the study was large and focused on many health endpoints, space on the questionnaire was at a premium and the forms were designed to be optically scanned. Therefore, we developed questions with discrete categorical response options. We assessed four menstrual outcomes: short cycles, long cycles, irregular cycles, and intermenstrual bleeding.

To classify menstrual cycle length, we asked women: "Many women have their periods (menstrual bleeding) about once a month. Some women have their periods more often and others less often. How often are your menstrual cycle periods? In other words, how many days are there from the first day of one menstrual period to the first day of the next period?" The answer categories were 24 days or less, 25–30 days, 31–35 days, 36–42 days, 43 days or more, or too irregular to say. We defined short cycles as 24 days or less, and long cycles as 36 days or more. These categories were selected based on the literature on menstrual cycle length.[2] Those who considered their menstrual periods "too irregular to say" were classified as having "irregular cycles." The comparison group for each of these three outcomes was women with periods between 25 and 35 days.

To assess intermenstrual bleeding we asked women: "During the past 12 months did you ever bleed or spot between menstrual periods? (Do not count spotting at the beginning or end of your period)." Women who answered "yes" were classified as having "intermenstrual bleeding."

Analysis

We first evaluated whether medical or lifestyle factors were associated with menstrual outcomes of interest using univariate analyses. Lifestyle variables included age, body mass, state, race, education, smoking, alcohol consumption, and age at menarche. Medical factors included self-reported history of physician-diagnosed rheumatoid arthritis, diabetes, stroke, high blood pressure treated with medication, depression treated with medication, goiter, "thyrotoxicosis/Graves disease/excess thyroid hormone," and "other thyroid disorders."

We then used logistic regression to simultaneously adjust for multiple potential risk factors for having each menstrual outcome. Our base logistic model included age and body mass index (BMI; weight [kg] per height squared [m^2]). Age was divided into five groups and BMI was divided into 8 groups. Both age and BMI were entered into the models as dummy variables to allow us to examine potential nonlinear relationships. Medical and lifestyle variables were added to the age/BMI model one at a time. Variables with odds ratios above 1.5, below 0.8, or with marginal statistical importance ($P <$ 0.2) were retained in the models for further testing.

To facilitate comparisons, we included the same covariates in the final models for each outcome. We next examined whether menstrual cycle characteristics were associated with nulligravity, infertility, or a previous fetal loss. We entered each of the four menstrual cycle patterns as independent variables in separate models for these three adverse reproductive outcomes. Infertility was defined as a history of having unprotected intercourse for more than a year without getting pregnant. Thus, it included women who had never been pregnant, those who previously had become pregnant but later had been unable to conceive, and women who had become pregnant after more than 1 year of trying. We restricted the fetal loss analysis to the most recent pregnancy of women who had been pregnant within the last 5 years. For this analysis, we grouped miscarriages, ectopic pregnancies, and stillbirths as fetal losses; other pregnancy outcomes, including induced abortions, served as the comparison group. Because age at menarche had no effect on infertility or fetal loss, we dropped it from those models. For the models of nulligravity and infertility, we controlled for current age. For the fetal loss models we

TABLE 1. Demographic, Lifestyle, Reproductive History, Medical History, and Menstrual Cycle Characteristics of 3941 Women age 21–40 in the Agricultural Health Study

Characteristic	Number* N = 3,941	Percent (%)
Demographic factors		
Age (years)		
21–25	122	3
26–30	536	14
31–34	1,032	26
35–37	1,042	26
38–40	1,209	31
Education		
Less than high school	59	2
High school	1,813	51
Some college	673	19
College degree or higher	1,018	29
Body Mass Index (kg/m^2)		
< 20	318	10
20–21	655	20
22–23	631	19
24–25	572	17
26–28	481	15
29–31	344	10
32–34	169	5
35+	152	5
Lifestyle factors		
Cigarette Smoking		
Never-smoker	2,805	72
Ex-smoker	638	16
Current smoker		
1–10 cigs/day	147	4
11–20 cigs/day	225	6
>20 cigs/day	88	2
Reproductive factors		
Age at menarche		
<12	562	14
12	1241	32
13	1215	31
14	576	15
15+	302	8
Parity		
0	369	9
1	456	12
2+	3112	79
Menstrual cycle characteristics		
Menstrual cycle length		
24 days or less (short cycle)	379	10
25–30 days	2765	71
31–35 days	456	12
36–42 days (long cycle)	88	2
>42 days (long cycle)	37	1
Too irregular to say	194	5
Intermenstrual bleeding (during last year)		
No mid-cycle spotting or bleeding	3399	87
Intermenstrual bleeding	520	13

* Missing data: education (N=378), BMI (N=619), smoking (N=38), age at menarche (N=45), parity (N=4), menstrual cycle length (N=22), intermenstrual bleeding (N=22).

controlled for age when most recent pregnancy ended, current BMI, and smoking during pregnancy

Results

Characteristics of Menstrual Cycles

Almost all women in the sample were white (98%) and most (78%) were from Iowa. Most were in their 30s, had two or more children, and had at least a high school education (Table 1). The prevalence of short cycles was 9.7%, long cycles 3.2%, and irregular cycles 5%. The prevalence of intermenstrual bleeding during the past year was 13.3%. Twenty-seven per cent of the women in the sample had at least one of the four menstrual patterns of interest. In many but not all analyses, exposures associated with long cycles were inversely associated with short cycles. For example, after adjusting for body mass and other covariates, the odds of short cycles increased with age, and odds of long cycles decreased with age (Figure 1). Women in their 30s were less likely to report irregular cycles. In contrast to the other outcomes, intermenstrual bleeding was not related to age (Figure 1). (The numerical results for Figures 1–4 are given in a table that is available with the electronic version of this article at http://www.epidem.com).

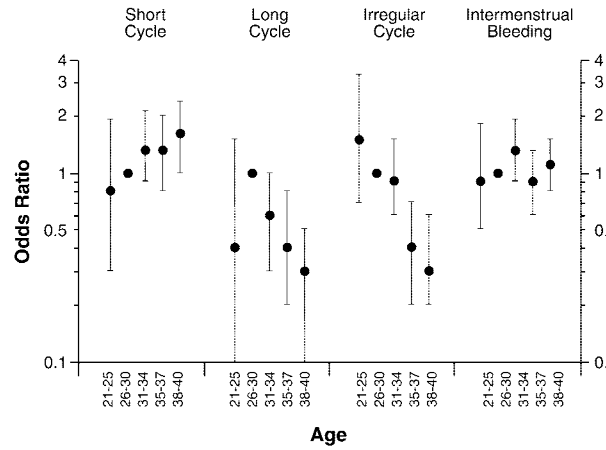

FIGURE 1. Relation between age and menstrual cycle characteristics. Y-axis is adjusted odds ratio on a log scale. *Black circles* are point estimates from a logistic model controlling for body mass index, age at menarche, smoking, Graves' disease, hypertension, depression, and diabetes. *Lines* above and below the point estimates are 95% confidence intervals. The referent group, women age 26–30, is represented by the *simple black circle* without confidence intervals.

Body Mass

Body fat, measured by BMI, was strongly associated with long cycles and irregular cycles (Figure 2). Women with high normal BMIs of 24–25 had twice the odds of long cycles compared with women with BMIs of 22–23, and the association grew stronger with each category of BMI. The odds of having a long cycle were five times higher among those with a BMI of 35 or higher (odds ratio [OR] = 5.4; 95% confidence interval [CI] = 2.1–13.7). Women in this heaviest group also showed increased odds of irregular cycles. There was a similar dose-response relation between BMI and odds of irregular cycles.

Menarche

Age at menarche before age 12 was moderately associated with increased odds of short cycles and intermen-

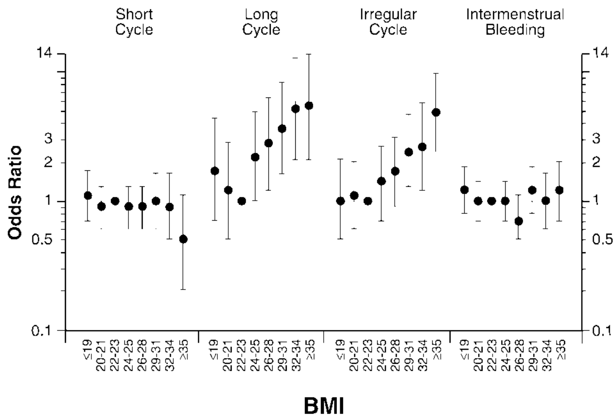

FIGURE 2. Relation between body mass index (BMI) and menstrual cycle characteristics. Y-axis is adjusted odds ratio on a log scale. *Black circles* are point estimates from a logistic model controlling for age, age at menarche, smoking, Graves' disease, hypertension, depression, and diabetes. *Lines* above and below the point estimates are 95% confidence intervals. The referent group, women with BMIs of 22–23, is represented by the *simple black circle* without confidence intervals.

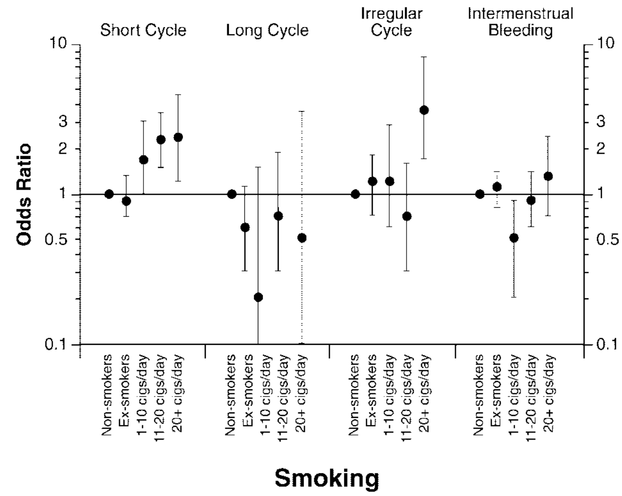

FIGURE 4. Relation between cigarette smoking and menstrual cycle characteristics. Y-axis is adjusted odds ratio on a log scale. *Black circles* are point estimates from a logistic model controlling for age, BMI, age at menarche, Graves' disease, hypertension, depression, and diabetes. *Lines* above and below the point estimates are 95% confidence intervals. The referent group, nonsmokers, is represented by the *simple black circle* without confidence intervals.

strual bleeding after adjusting for covariates (Figure 3). Having a late age of menarche (age 15 or older) was associated with almost three times the odds of long cycles and about a doubling in the odds of irregular cycles.

Smoking

Cigarette smoking was associated with short cycles and with irregular cycles (Figure 4). The odds of having irregular cycles were 3.6 among women who smoked more than a pack a day compared with nonsmokers (95% CI = 1.7–8.0).

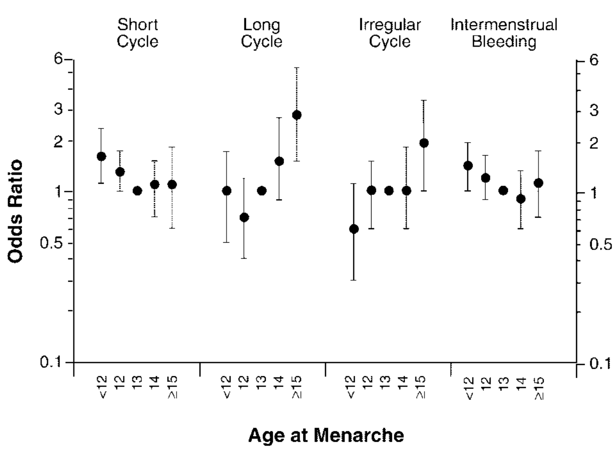

FIGURE 3. Relation between age at menarche and menstrual cycle characteristics. Y-axis is adjusted odds ratio on a log scale. *Black circles* are point estimates from a logistic model controlling for age, BMI, smoking, Graves' disease, hypertension, depression, and diabetes. *Lines* above and below the point estimates are 95% confidence intervals. The referent group, women with age of menarche at age 13, is represented by the *simple black circle* without confidence intervals.

Medical Disorders

Self-reported history of Graves' disease was associated with more than a four-fold increase in odds of long cycles (Table 2). Depression treated with medication was associated with about a doubling of intermenstrual bleeding, irregular cycles, and long cycles. History of diabetes was associated with increased odds of irregular and long cycles. We did not have enough cases to analyze diabetes by age of onset or more detailed data to distinguish between type 1 and type 2 diabetes. History of drug-treated high blood pressure, rheumatoid arthritis, stroke, goiter, and other thyroid disorders was not associated with menstrual cycle patterns.

Reproductive Outcomes

Having irregular cycles was associated with increased odds of never having been pregnant (Table 3). Long or irregular cycles were each associated with more than twice the odds of infertility. Intermenstrual bleeding was also associated with increased odds of infertility. Long and irregular cycles were each associated with about a doubling in odds of fetal loss in the most recent pregnancy of women reporting a pregnancy within the past 5 years, after adjusting for current body mass, age, and smoking when the pregnancy ended.

TABLE 2. Relation Between History of Self-Reported, Physician-Diagnosed Medical Conditions and Menstrual Cycle Characteristics*†

		Short cycle		Long cycle		Irregular cycle‡		Intermenstrual bleeding	
	N	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Graves disease	28	2.6	0.9–7.4	4.5	1.2–16.8	(no cases§)		1.9	0.7–4.9
High blood pressure requiring medication	137	0.8	0.4–1.7	1.0	0.3–3.1	1.2	0.5–2.8	1.5	0.9–2.5
Depression requiring medication	234	0.9	0.6–1.6	1.8	0.9–3.6	1.9	1.1–3.4	2.1	1.5–3.0
Diabetes	49	0.9	0.3–3.0	1.5	0.3–7.1	2.1	0.7–6.5	1.3	0.6–3.2

* Adjusted for age (5 categories), body mass index, age at menarche, current smoking, Graves'disease, hypertension, depression and diabetes.
† Comparison group for each set of medical conditions is all women in the dataset who do not have the condition.
‡ Menstrual cycle pattern was too irregular to give a usual cycle length.
§ There were no cases of Graves'disease among women with irregular cycles, and so the irregular cycles models did not adjust for this outcome.

Discussion

Our data are consistent with studies reporting that mean menstrual cycle length shortens after age 20 and menstrual cycle variability decreases as women age up to the onset of the menopausal transition.[6,12,15]

The literature suggests that risk of long or irregular cycles increases at both extremes of the weight distribution.[1,10,16,17] However, only limited information is available on the risk of long or irregular cycles among women with intermediate body size. Ours is one of the first studies to show such a clear dose-effect relation between BMI and long or irregular cycles. A cross-sectional study of 26,000 women in a weight-loss program also reported linear relations between weight (BMI not measured) and odds of long or irregular cycles.[18] A smaller, prospective study by Symons *et al.*[19] reported a J-shaped relation between body mass and cycle length (but not with irregular cycles). In both the Symons study and ours, odds of a long cycle increased in a stepwise manner at BMIs above 23. Our data also resemble the J-shaped relation reported by Symons *et al.*, although the confidence interval for the elevated odds of long cycles among thin women did not exclude 1.0.

We found that onset of menses before age 13 was associated with short cycles and intermenstrual bleeding for women at age 21–40. Menarche at age 15 or later was associated with having long cycles and irregular cycles. In a study of women age 12–14 followed prospectively for 2 years, investigators reported a similar pattern; late age of menarche was associated with longer mean cycle length and increased menstrual cycle variability.[20] The relation between age of menarche and subsequent menstrual cycle characteristics among adult women could result from continued exposure to factors such as intense exercise.[16] Alternatively, the sensitivities of biological feedback systems and mechanisms controlling bleeding may be set before puberty and then affect both age at menarche and adult menstrual patterns.

Some studies have reported more frequent, short cycles among smokers[21] or heavy smokers,[22] although several studies did not find associations between smoking and cycle length.[23,24] Our data support an association, with even moderate smokers having increased odds of short cycles. Most previous studies (but not all)[24] have reported increased menstrual cycle variability among smokers,[21] particularly heavy smokers.[22,23] We found an association between heavy smoking and irregular cycles that was not apparent for lighter smokers (Figure 4).

There are only limited data on the menstrual characteristics of women with chronic diseases. Long cycles are commonly reported among women with Graves' disease; short cycles are a less common complication.[25]

Table 3. Relation Between Menstrual Cycle Characteristics and Risk of other Reproductive Outcomes

		Short cycle		Long cycle		Irregular cycle		Intermenstrual bleeding	
	N*	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Never pregnant†	306	1.0	0.6–1.6	0.6	0.2–1.3	1.5	0.9–2.5	1.1	0.8–1.7
Infertility‡,§	1041	0.8	0.6–1.0	2.4	1.6–3.5	2.8	2.0–3.9	1.7	1.3–2.1
Fetal loss for most recent pregnancy‖,¶	135	0.4	0.1–1.3	2.3	0.9–5.7	1.9	0.8–4.4	1.3	0.7–2.4

* N in column heading is the total number of reproductive events in the dataset. N's in the adjusted models varied with different menstrual characteristics. For never pregnant, N was 229 for short cycle, 214 for long cycle, 231 for irregular cycle, and 257 for intermenstrual bleeding. For infertility, N was 738 for short cycle, 721 for long cycle, 749 for irregular cycle, and 864 for intermenstrual bleeding. For fetal loss, N was 96 for each model.
† Adjusted for age as a continuous variable, body mass, and smoking.
‡ Adjusted for age as continuous variable, body mass, and smoking.
§ History of trying to become pregnant for more than 12 months or taking over 12 months to become pregnant.
‖ History of fetal loss (spontaneous abortion, ectopic pregnancy, or stillbirth) during most recent pregnancy among women who had a pregnancy within the past five years. Women who had never been pregnant during the past 5 years were excluded from the models.
¶ Adjusted for age when most recent pregnancy ended (age and age squared), current body mass, and cigarette smoking during pregnancy.

Our data are consistent with these observations. However, because we did not ask women whether they had ever had a medical evaluation for a menstrual problem, we are unable to rule out detection bias as a possible explanation. It is possible that women who had unusual menstrual cycle patterns were simply more likely to have had a thyroid function test.

In our data, diabetes was associated with increased odds of long and irregular cycles after adjusting for BMI and other covariates, although the confidence intervals for these associations were wide. In a cross-sectional study such as ours, the direction of causality is ambiguous. A Danish study of menstrual cycle patterns among diabetic women reported a four-fold increase in having menarche at age 17 or later (primary amenorrhea) and increased risk of secondary amenorrhea (6 months or longer without a period), long cycles, and irregular cycles.[26] In addition, in the Nurses' Health Study, women with long or irregular menstrual cycles had a doubling in risk of developing type 2 diabetes mellitus after adjusting for BMI.[27]

In our data, drug-treated depression was associated with increased odds of intermenstrual bleeding, irregular cycles, and long cycles. These associations might be attributable to increased stress among depressed women, to depression itself, or to the medication treatment for depression. We did not have data to clarify this further.

The underlying biology and mechanisms affecting menstrual cycle characteristics has not been well described. Variation in length of the follicular phase is responsible for most of the variability in cycle length, and follicular phase length depends on a process of follicular maturation and selection of the primary follicle. Both are dependent on FSH from the pituitary and appropriate ovarian response. Short and long cycles are more likely to be anovulatory than cycles of 25–35 days.[1] Women with highly variable cycle lengths are also more likely to have anovulatory cycles.[8] Both heavy and light women are more likely to have anovulatory cycles than women of intermediate body weight.[1,8] It would also be of interest to pursue the role of insulin sensitivity in the association between BMI and cycle characteristics. Clinical insulin resistance and elevated androgen levels were associated with long cycles among Pima Indians,[29] and long and irregular cycles were associated with risk of developing type 2 diabetes in the Nurses Health Study.[27]

These data have some important limitations. We restricted our analysis to women who had completed two questionnaires and met a strict set of reproductive criteria, which raises concerns about possible biases. We tried to evaluate this, first by comparing women who answered both questionnaires with those who only completed the exposure questionnaire. We found that the distribution of demographic characteristics such as age, education, BMI, or number of children (as reported on the husband's enrollment questionnaire) were similar in both groups. About one-fifth of the women who otherwise met the age criteria for inclusion were taking oral contraceptives. Women on oral contraceptives do not menstruate and thus cannot provide information on menstrual characteristics. However, because oral contraceptives are often prescribed for women who are having menstrual irregularities, our data may underestimate the prevalence of long or irregular cycles in our population. Selection bias could also have resulted if women chose to participate both because they had menstrual problems or related reproductive outcomes such as infertility and because they experienced the exposures of interest. Because we evaluated many exposures, we think this is an unlikely source of systematic bias.

Several other design limitations deserve comment. Because this was a study of women living on farms, there is a possible problem with generalizing our study results to other populations of women. We did not have data on stress or physical activity, both of which are important risk factors for menstrual cycle irregularities.[1,2,10,28] Although we omitted from analysis women who were currently breast feeding, pregnant, or taking oral contraceptives, we could not identify women who had recently stopped breast feeding, taking oral contraceptives, or ended a pregnancy, and they may have had cycles that did not reflect their typical patterns. Our measures of thyroid disease, diabetes, and other chronic diseases were based on self-report. Finally, the data were cross-sectional so the associations we observed may not be causal.

Despite these limitations, this is one of the largest studies of menstrual function among adult women in the United States, and our findings suggest some important new avenues for research on factors that may perturb menstrual function.

This paper is also one of the few papers to evaluate the association of self-reported menstrual cycle characteristics with other adverse reproductive outcomes. Women with irregular cycles were less likely to have ever been pregnant. Except for short cycles, every one of our menstrual cycle parameters was associated with a history of infertility. A California study of urinary biomarkers and menstrual function reported that women with current anovulatory cycles were four times as likely to have had difficulty becoming pregnant in the past.[22] In our data, long cycles and irregular cycles were associated with increased odds of prior fetal loss. Although these relations should be further investigated in a prospective study, it is likely that exposures or risk factors that perturb normal menstruation also may increase a woman's risk of other reproductive disorders.

This paper has demonstrated that menstrual patterns are influenced by a number of host and environmental characteristics. Importantly, these data suggest that even small increases in BMI have observable impacts on menstrual patterns. The increase in obesity in the United States and elsewhere increases the risk of reproductive problems as well as the risk of chronic disease. Menstrual cycle patterns result from biological systems that depend upon a woman's hormonal status and that are sensitive to environmental influences. Therefore, factors that disrupt menstruation should be suspected of being capable of disrupting normal reproductive function. Identifying differences in women's menstrual cycle characteristics, and understanding more about the determinants of those differences and their association to other reproductive outcomes, may yield important insights into women's reproductive biology.

Acknowledgments

We thank Cheryl McDonnell for her help managing the Agricultural Health dataset and Pam Schwingl, Sheila Zahm, and Glinda Cooper for their helpful comments, which improved the manuscript.

References

1. Harlow SD. Menstruation and menstrual disorders: the epidemiology of menstruation and menstrual dysfunction. In: Goldman MB, Hatch MC, eds. *Women and Health*. San Diego: Academic Press, 2000;99–113.
2. Harlow SD, Ephross SA. Epidemiology of menstruation and its relevance to women's health. *Epidemiol Rev* 1995;17:265–286.
3. Cooper GS, Sandler DP. Long-term effects of reproductive-age menstrual cycle patterns on peri- and postmenopausal fracture risk. *Am J Epidemiol* 1997;145:804–809.
4. Cooper GS, Ephross SA, Weinberg CR, Baird DD, Whelan EA, Sandler DP. Menstrual and reproductive risk factors for ischemic heart disease. *Epidemiology* 1999;10:255–259.
5. Ellison PT, Cabot TD. Human ovarian function and reproductive ecology: new hypotheses. *Am Anthropol* 1990;92:933–952.
6. Treloar AE, Boynton RE, Behn B, Brown BW. Variation of the human menstrual cycle through reproductive life. *Int J Fertil* 1967; 12:77–126.
7. Chiazze L, Brayer FT, Macisco JJ, Parker MP, Duffy BJ. The length and variability of the human menstrual cycle. *JAMA* 1968;203: 377–380.
8. Waller K, Swan SH, Windham GC, Fenster L, Elkin EP, Lasley BP. Use of urine biomarkers to evaluate menstrual function in healthy premenopausal women. *Am J Epidemiol* 1998;147:1071–1080.
9. Harlow SD, Campbell B. Host factors that influence the duration of menstrual bleeding. *Epidemiology* 1994;5:352–355.
10. Harlow SD, Matanowski GM. The association between weight, physical activity, and stress and variation in the length of the menstrual cycle. *Am J Epidemiol* 1991;133:38–49.
11. Vollman RF. *The Menstrual Cycle*. Philadelphia: Saunders, 1977.
12. Matsumoto S, Nogami Y, Ohkuri S. Statistical studies of menstruation: a criticism on the definition of normal menstruation. *Gunma J Med Sci* 1962;11:294–318.
13. Alavanja MCR, Akland G, Baird DD, *et al.* Cancer and noncancer risk to women in agriculture and pest control: the agricultural health study. *J Occup Med* 1994;36:1247–1250.
14. Alavanja MCR, Sandler DP, McMaster SB, *et al.* The agricultural health study. *Environ Health Perspect* 1996;104:362–369.
15. Harlow SD, Lin X, Ho MJ. Analysis of menstrual diary data across the reproductive life span; applicability of the bipartite model approach and the importance of within-woman variance. *J Clin Epidemiol* 2000;53:722–733.
16. Bullen BA, Skrinar GS, Beitins IZ, von Mering G, Turnbull BA, McArthur JW. Induction of menstrual disorders by strenuous exercise in untrained women. *N Engl J Med* 1985;312:1349–1353.
17. Schweiger U, Laessle R, Pfister H, *et al.* Diet-induced menstrual irregularities: effects of age and weight loss. *Fertil Steril* 1987;48: 746–751.
18. Hartz AJ, Barboriak PN, Wong A, Katayama KP, Rimm AA. The association of obesity with infertility and related menstrual abnormalities in women. *Int J Obes* 1979;3:57–73.
19. Symons JP, Sowers MR, Harlow SD. Relationship of body composition measures and menstrual cycle length. *Ann Hum Biol* 1997;24:107–116.
20. Harlow SD, Campbell B, Lin X, Raz J. Ethnic differences in the length of the menstrual cycle during the postmenarcheal period. *Am J Epidemiol* 1997;146:572–580.
21. Brown S, Vessey M, Stratton I. The influence of method of contraception and cigarette smoking on menstrual patterns. *Br J Obstet Gynecol* 1988;95:905–910.
22. Windham GC, Elkin EP, Swan SH, Waller KO, Fenster L. Cigarette smoking and effects on menstrual function. *Obstet Gynecol* 1999;93:59–65.
23. Hornsby PP, Wilcox AJ, Weinberg CR. Cigarette smoking and disturbance of menstrual function. *Epidemiology* 1998;9:193–198.
24. Cooper GS, Sandler DP, Whelan EA, Smith KR. Association of physical and behavioral characteristics with menstrual cycle patterns in women age 29–31 years. *Epidemiology* 1996;7:624–628.
25. Doufas AG, Mastorakos G. The hypothalamic-pituitary-thyroid axis and the female reproductive system. *Ann N Y Acad Sci* 2000;900:65–76.
26. Kjær K, Hagen C, Sando SH, Eshoj O. Epidemiology of menarche and menstrual disturbances in an unselected group of women with insulin-dependent diabetes mellitus compared to controls. *J Clin Endocrinol Metab* 1992;75:524–529.
27. Solomon CG, Hu FB, Dunaif A, *et al.* Long or highly irregular menstrual cycles as a marker for risk of type 2 diabetes mellitus. *JAMA* 2001;286:2421–2426.
28. Fenster L, Waller K, Chen J, *et al.* Psychological stress in the workplace and menstrual function. *Am J Epidemiol* 1999;149:127–134.
29. Weiss DJ, Charles MA, Dunaif A, Prior DE, Lillioja S, Knowler WC. Hyperinsulinemia is associated with menstrual irregularity and altered serum androgens in Pima Indian women. *Metabolism* 1994;43:803–807.